Internal Dosimetry: State of the Art and Research Needed

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ABSTRACT

Internal dosimetry is a discipline which brings together a set of knowledge, tools and procedures for calculating the dose received after incorporation of radionuclides into the body. Several steps are necessary to calculate the committed effective dose (CED) for workers or members of the public. Each step uses the best available knowledge in the field of radionuclide biokinetics, energy deposition in organs and tissues, the efficiency of radiation to cause a stochastic effect, or in the contributions of individual organs and tissues to overall detriment from radiation. In all these fields, knowledge is abundant and supported by many works initiated several decades ago. That makes the CED a very robust quantity, representing exposure for reference persons in reference situation of exposure and to be used for optimization and assessment of compliance with dose limits. However, the CED suffers from certain limitations, accepted by the International Commission on Radiological Protection (ICRP) for reasons of simplification. Some of its limitations deserve to be overcome and the ICRP is continuously working on this. Beyond the efforts to make the CED an even more reliable and precise tool, there is an increasing demand for personalized dosimetry, particularly in the medical field. To respond to this demand, currently available tools in dosimetry can be adjusted. However, this would require coupling these efforts with a better assessment of the individual risk, which would then have to consider the physiology of the persons concerned but also their lifestyle and medical history. Dosimetry and risk assessment are closely linked and can only be developed in parallel. This paper presents the state of the art of internal dosimetry knowledge and the limitations to be overcome both to make the CED more precise and to develop other dosimetric quantities, which would make it possible to better approximate the individual dose.

Keywords: Internal Dosimetry, Committed Effective Dose, State of the Art, Gaps

Review

Introduction

Internal dosimetry is a discipline which brings together a set of knowledge, tools and procedures for calculating the dose received after intake of radionuclides. Although this expression is somewhat inappropriate, the term is commonly used to distinguish it from external dosimetry, which refers to the dose received after external exposure, i.e., when the sources are outside the body. Internal dosimetry was historically developed to allow the calculation of doses to workers after occupational exposures [1, 2]. It was then extended to the whole population [3], and, more recently, to non-human organisms, living in a contaminated environment [4].

There are many tools available for determining the doses after internal contamination, most of them being developed decades ago. These tools have shown all their advantages over the past years for calculating doses for both workers and members of the

public. However, they also have some limitations, which require improvement. This paper aims to present the state of the art in the field of internal dosimetry and to highlight the areas where some research is still needed.

Methods for Determining Doses After Internal Contamination

An adequate assessment of internal exposure resulting from intakes of radionuclides is essential for the optimization of exposures, assessment of the health consequences from releases of radioactivity in a workplace or in the environment, and prospective or retrospective demonstration of compliance with regulatory requirements. After the intake of radionuclides, doses received by organs and tissues are protracted, so equivalent and effective doses are accumulated over time. The resulting quantities are referred to as committed doses. Calculating committed effective dose (CED) is a complex procedure and can be done using two different methods (Fig. 1).

In the first method, CED is calculated from the knowledge of the intake, which is the main determinant of the dose. The first step in the method is to define the radionuclide deposition and retention in tissues, which depend on physiological factors such as breathing rate for intake by inhalation for ex-

ample, and on many abiotic factors including the physical and chemical form of the radionuclide when incorporated into the body. Long retention in the organs and tissues increases the probability of radionuclide disintegration and therefore increases the dose. The radionuclide behavior in the body is predicted using biokinetic models which describe the organ and tissue deposition according to the chemical form of the radionuclides, as well as their transfer rate from one organ or tissue to another. The second step of the method is to determine the number of nuclear transformations in each model compartment (i.e., organ, part or group of organs sharing the same characteristics) over time of activity retention, and then the energy emitted during these decays. This is given using types, energies, and mean numbers of particles emitted per nuclear transformation (yields) or radiations emitted in spontaneous nuclear transformation, which are provided in the literature [5]. Then, phantoms (computer models of the human anatomy) and codes for simulation of radiation-matter interaction are used to calculate the absorbed dose in the tissues. The relevant weighting factor for radiation is used to calculate the committed equivalent dose to the organs and finally the tissue weighting factors are used to calculate the CED [6].

The second way of calculating the CED is to start from the measurement of activity in the whole body, in organs, or in
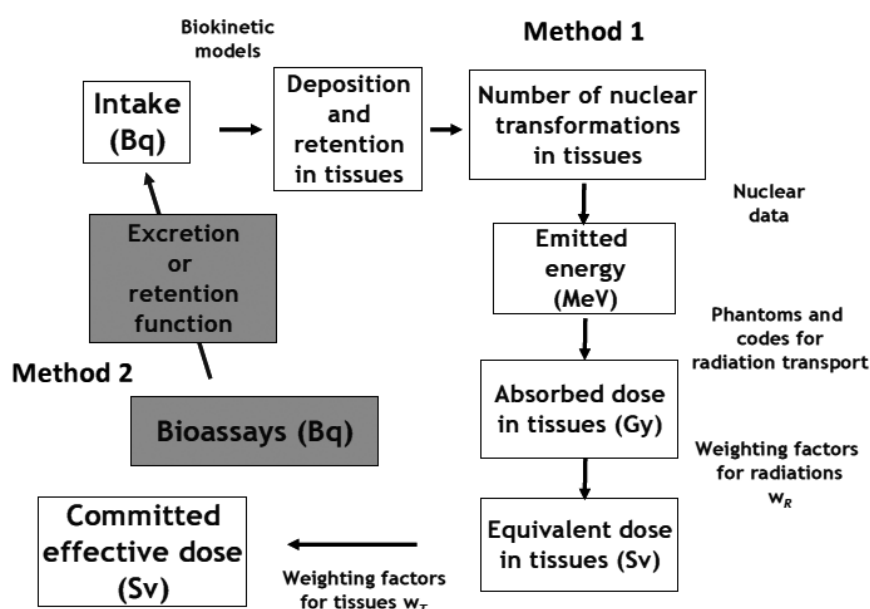
Fig. 1. Schematic representation of the two methods available for calculating doses after internal contamination. Method 1 (white squares) starts from the knowledge of the intake and, using biokinetic models, nuclear data, phantoms, codes for radiation transport, and weighting factors allows to calculate the committed effective dose (CED). Method 2 (grey squares) starts from the activity in the bioassays and, using excretion and retention functions allows to calculate the intake and then, using method 1, to determine the CED.

excreta. This second method is widely used when the intake is unknown and applies mainly to workers. In this method, data on radionuclide content in the excreta or in some organs such as the thyroid or lungs are compared with reference excretion or retention functions, which are built from the biokinetic models described above. Knowing the time elapsed between the exposure and the measurement, this method first estimates the intake, then calculates the CED as described in the first method.

Whatever the method, the procedure is long, complex and restricted to some experts. Two simplified procedures can be used for both methods, depending on the available data. Knowing the intake, the CED can be directly calculated by using CED coefficients (Fig. 2). These coefficients, provided by the International Commission on Radiological Protection (ICRP) for workers, members of the public, and many chemical forms and scenarios of exposure (route of contamination, particle size, acute or chronic intake, etc.), allow the direct calculation of the dose by simply multiplying the intake, in Bq, by the coefficient, given in Sv Bq^{-1} [7]. The coefficients consider every step described in Fig. 1 and represent an easy and rapid way to calculate doses, accessible to any person in charge of radiological protection. They are provided for every radionuclide commonly encountered.

When intake is unknown and dose needs to be calculated from bioassay data (i.e., method 2), dose per content functions [7] may be used, allowing direct determination of the

CED from the activity obtained by the given bioassay method, depending on the time elapsed between the exposure and measurement. In such a case, simple multiplication of the dose per content data by the activity in the excreta or in the body (whole body or in specific organs such as the thyroid or lungs) gives the CED.

The CED coefficients and dose per content functions may be used for both prospective and retrospective assessments of exposure. They are, however, given for reference persons and reference exposure situations, for the purpose of radiological protection. Prospective assessments provide estimates of intakes and resulting doses for reference workers engaged in specific activities or for reference members of the public exposed in specific circumstances, using information on projected exposures to radionuclides. These assessments generally make use of default assumptions about exposure conditions and default values for parameters describing material-specific properties, such as the particle size distribution of an inhaled aerosol or the absorption characteristics of a material after inhalation or ingestion. Retrospective assessments use the results of individual monitoring and workplace monitoring to assess doses in order to maintain individual dose records and demonstrate compliance with regulatory requirements.

The procedure for determining internal doses for non-human biota is strictly identical to that of humans, with required knowledge of the intake, assessment of deposition and retention in the tissues, and calculation of energy deposition in every tissue. The only difference is that CED is a concept that was created for the management of exposure in humans, which is strongly linked to the risk of developing stochastic effects (i.e., cancer and hereditary effects). For non-human biota, it is therefore requested to stop the procedure at the step where the absorbed dose rate in an organ or in the whole body is calculated [4]. If needed, this absorbed dose rate may be weighted according to the efficiency of specific radiation to cause damage, using the relative biological effectiveness (RBE, see more details below). The obtained quantity is then the RBE-weighted absorbed dose rate [4].
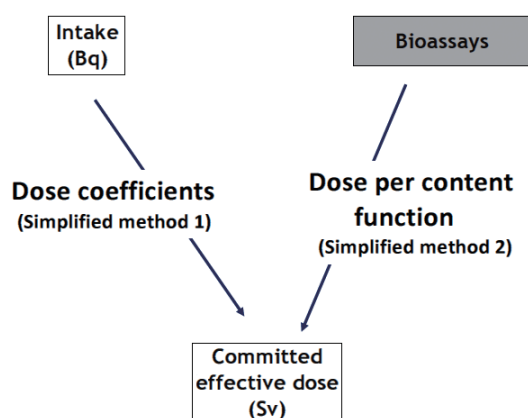
State of the Art

Tools and concepts in internal dosimetry were developed decades ago and are now very sophisticated. In each step depicted in Figs. 1 and 2, progress has been made over the years to develop more precise models for more accurate de-

Fig. 2. Representation of two simplified ways to calculate doses after internal contamination. In the simplified method 1, dose coefficients provided by International Commission on Radiological Protection allow to calculate directly the committed effective dose (CED) from the knowledge of the intake. These coefficients consider every step described in Fig. 1. Similarly, in the simplified method 2, dose per content functions allow a direct assessment of the CED from the knowledge of the activity in the bioassays.

termination of the dose. Up-to-date data and models are described in the latest ICRP documents [5, 7–16]. General guidance on how to use these models and data was also published by several bodies [17–20]. This paper aims to highlight certain features of the models without claiming to be exhaustive. In this work, knowledge about the effect of radiation on the body will not be discussed, although dosimetry and health effects are strongly related, mainly because doses are calculated to address the risk of stochastic effects.

1. Biokinetic Models

As stated above, biokinetic models describe the time-dependent deposition and retention of radionuclides in organs and tissues, and, by extension, the excretion from the body. Many models are available, produced initially to describe the behavior in workers, of the most common radionuclides and chemical forms found in nuclear workplaces [21–24]. Since the Chernobyl accident, the number of radionuclides considered in the models has considerably increased, in parallel with the development of more physiologically realistic models which now describe the deposition, retention, recycling and excretion of radionuclides in workers, but also in members of the public, including children at different ages, embryos and fetuses [25–31]. The latest series of ICRP documents, dedicated to occupational intakes of radionuclides (OIR series), now provides models for contamination by most elements from the periodic table, except for some noble gases (He, Ne, Ar, Kr, and Xe) which are considered to be irrelevant for contamination by inhalation [7, 9–12]. To complete this new set of data, ongoing work on models for members of the public will provide age-dependent data for the same elements and for additional chemical forms, including organic forms in diet (environmental intakes of radionuclides [EIR] series, pending).

The data used to build these models come mainly from animal experiments and/or from follow-up of occupational exposure and patients of nuclear medicine. Their diversity allows the construction of several types of models. Some of them describe the entry of radionuclides into the body and then, after absorption, other (systemic) models describe the behavior of radionuclides in the blood and in the organs (Fig. 3).

Models of entry are the human respiratory tract model (HRTM) [32], the human alimentary tract model (HATM)
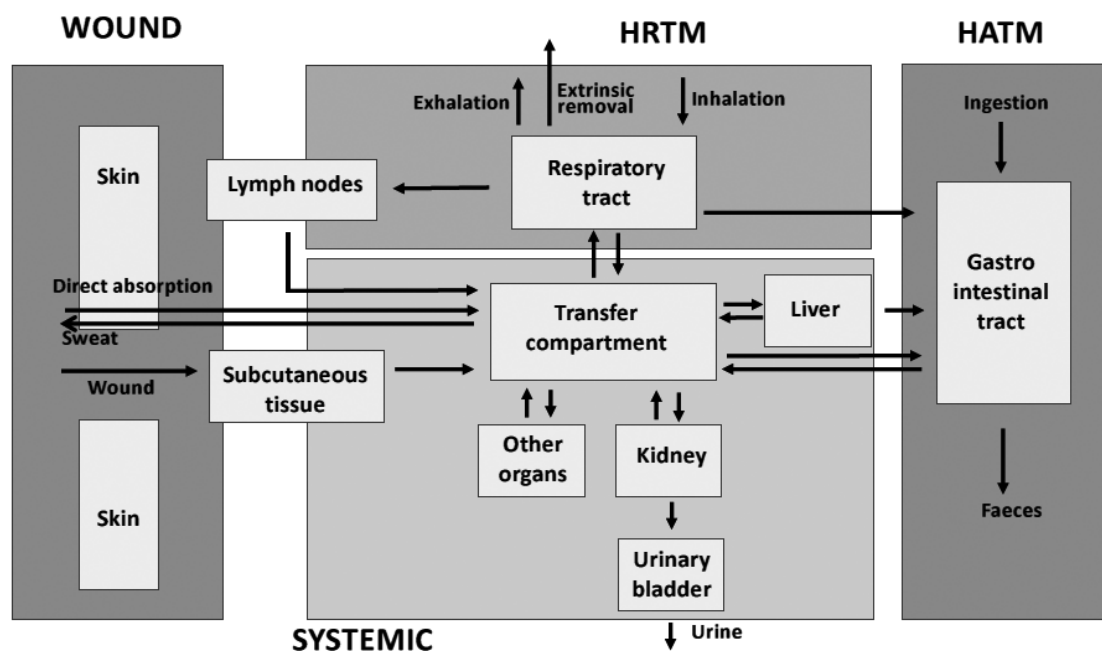

Fig. 3. Schematic representation of the biokinetic models provided by International Commission on Radiological Protection and National Council on Radiation Protection and Measurements. The human respiratory tract model (HRTM) provides age-specific data for deposition and material-specific data for translocation to blood. The human alimentary tract model (HATM) provides age- and gender-specific transit times for all segments of the alimentary tract and, for oral cavity, esophagus and stomach, also provides material-specific transit times. The wound model describes deposition and clearance from a wound. Systemic models describe the time-dependent distribution and retention of a radionuclide in the body after it reaches the systemic circulation, and its excretion. Redrawn from [27].

[13] and the wound model [33]. These models are material-specific, i.e., they provide data on deposition and transfer to blood according to the solubility of the elements, which in turn depend on their physical and chemical form.

- The HRTM provides age-specific data for deposition and material-specific data for translocation to blood [7, 32]. Inhaled particles containing radionuclides are deposited in the extra-thoracic airways (nose, larynx, etc.), the bronchial and bronchiolar airways of the lung and the alveolar-interstitial region, with deposition in each region being mainly dependent on particle size. Removal from the respiratory tract occurs mainly by dissolution and absorption into blood, transfer to regional lymph nodes, and the competing mechanical transport of particles by muco-ciliary clearance up to the throat, followed by their entry into the alimentary tract. The proportions absorbed into the blood or cleared by particle transport depend on the speciation and the solubility of the material, and on the radioactive half-life of the radionuclide. The HRTM is also applied to gases and vapors, and in the OIR series, to inhalation of radon and its radioactive progeny [10].

- The HATM provides age- and gender-specific transit times for all segments of the alimentary tract and, for the upper segments (oral cavity, esophagus, and stomach), also provides material-specific transit times [13]. A default assumption is made that absorption of an element and its radioisotopes into the blood occurs exclusively in the small intestine. However, the model structure allows for the inclusion of other sites of absorption where information is available. The model also allows for retention in the mucosal tissues of the walls of alimentary tract regions and on teeth where information is available.

- The wound model was produced by the National Council on Radiation Protection and Measurements (NCRP) [33]. It describes the deposition and clearance that is suitable for calculating radiation doses to skin, subcutis tissue, muscle, and other organs and tissues. The wound model comprises seven compartments, of which five describe radionuclide behavior at the wound site (given as fragment; soluble; colloid and intermediate state; particles, aggregates and bound state; trapped particles and aggregates) and two can receive radionuclides transported from the wound site (blood and lymph nodes). The compartments that come into play

for any given wound depend on the physico-chemical properties of the radionuclides in the wound. The transfer of material between compartments is characterized using first-order rate constants, which were empirically found to be adequate for describing the available data set. Dose coefficients for local doses are presented for 48 elements. The wound model is not intended for the calculation of the formal CED since wounds result from an accident, which, by definition, cannot be managed according to the principles of optimization and limitation.

Systemic models describe the time-dependent distribution and retention of a radionuclide in the tissues of the body after it reaches the systemic circulation (mainly blood), and its excretion in urine and feces. In an ideal world, these models would be element-specific regarding model structure as well as parameter values because the behavior of the radionuclides in the body is governed by their chemical affinity towards biological structures. However, several generic model structures were used in previous ICRP documents to address the systemic biokinetics of groups of elements, typically chemical families, known to have qualitatively similar behavior in the body. For example, ICRP publication 20 [34] introduced a generic model formulation for the alkaline earth elements calcium, strontium, barium and radium, but provided element-specific values for most model parameters. In ICRP publication 30 series [21–24], a model developed for plutonium, including parameter values as well as model structure, was applied to most actinide elements. The use of generic systemic model structures increased in ICRP reports on doses to members of the public from intake of radionuclides [25–28] and is further expanded in new reports because it facilitates the development, description, and application of systemic biokinetic models. An important development is that, when the availability of data is allowed, models have been made to be more physiologically realistic with regard to the dynamics of organ retention and excretion so that they are applicable to the interpretation of bioassay data as well as the calculation of dose coefficients.

2. Retention and Excretion Functions for Bioassay Interpretation

It was stated above that doses from intakes of radionuclides can also be assessed retrospectively from bioassay measurements (e.g., daily urinary and fecal excretion) or from measurements of the radionuclides in the body or in

parts of the body. ICRP publications 54 and 78 gave guidance on the design of monitoring programs and the interpretation of results to estimate doses to workers following radionuclide inhalation or ingestion [35, 36]. The guidance was supported by numerical data to enable the assessment of intakes and doses from bioassay data. These data were provided for a number of radionuclides selected as most likely to be encountered in the workplaces. Predicted values of the measured quantities for various times after a single intake or for routine monitoring allow the calculation of the incorporated activity. Standard dose coefficients must then be used to calculate CED from the assessed intake.

Significant progress was made during the last decade with the provision of dose per content functions that allow direct determination of the CED from the knowledge of the activity in a given bioassay, and the time elapsed between the exposure and the measurement. The main advantage of this approach is that the user does not perform the intermediate step of calculating the intake in order to evaluate the dose. Dose per content functions are largely insensitive to the choice of inhaled particle size for a wide range of measurement times following intakes [37]. These data may also be insensitive to the choice of absorption type for the specific chemical form involved, for specific measurement times after the intake, and this dramatically reduces the risk of error. All of this makes the determination of doses from bioassays more reliable and faster. Dose per content functions are now given for the exposure of workers to most elements from the periodic table, excluding some noble gases, as stated above [7, 9–12]. Dosimetric data for exposure from submersion in a cloud made of neon, argon, krypton, and xenon are however given in Annex A of ICRP publication 151 [12].

3. Calculation of Nuclear Transformations and Energy Emitted in Organs and Tissues

Biokinetic models for individual elements and their radioisotopes are used to calculate the total number of nuclear transformations (radioactive decays) occurring within specific tissues, organs, or body regions during a given period of time (usually 50 years for adults, or to age 70 years for children) by determining the time-integrated activity in each source region [7].

The number of transformations in tissues and the associated emitted energy are calculated using nuclear data for radionuclides. These data were updated in ICRP publication 107 [5], which provides an electronic database of the physical data needed to calculate radionuclide-specific protection and operational quantities. The database contains information on the half-lives, decay chains, and yield and energy of radiation emitted in nuclear transformations of 1,252 radionuclides of 97 elements. Nuclides were selected for consideration if their half-life exceeded 10 minutes, if they are formed through nuclear transformation of a selected radionuclide or if they are of potential interest to nuclear medicine. This database represents a comprehensive set of data and fully meets the calculation needs for the purpose of internal dosimetry.

4. Use of Numerical Phantoms and Codes for Radiation Transport

The calculation of energy deposition in tissues is obtained using specific codes for radiation transport that simulate radiation-matter interaction in the anatomy modeled by computational phantoms of different ages and sex. Numerical phantoms have replaced the old, stylized phantoms [38, 39] (e.g., mathematical models) allowing a more precise determination of the energy deposition in every organ. Voxel phantoms were first developed during the 90s and are three-dimensional representations of human anatomy [40]. They allow the calculation of absorbed dose in each of the 2 to 4 million voxels comprising the adult male or female phantoms. These phantoms, built from tomographic imaging data of real male and female patients, were segmented (i.e., organ borders were delimited on the anatomical images) and then adjusted to the reference male and female from ICRP (i.e., organ size, shape, density, and elemental composition of organs are defined in the phantoms according to ICRP publication 89 data [41]).

In recent years, a new series of phantoms was developed to address the limitation of the voxel resolution, especially with respect to small tissue structures (e.g., the lens of the eye) and very thin tissue layers (e.g., stem cell layers in the stomach wall mucosa and intestinal epithelium). These new phantoms, called "mesh-type reference computational phantoms," include all source and target regions needed for estimating the effective dose, including the micrometer-thick target region in the respiratory and alimentary tract organs, skin and urinary bladder. These mesh-type phantoms are produced for adult reference male and female [16] and are going to be produced soon for children at different ages, and for the embryo and fetus at different gestational stages.

These models are used to provide reference radiation transport data in the form of specific absorbed fraction (SAFs) for

radiation emitted from radionuclides retained in body organs and tissues [14]. SAFs represent the deposition of energy in all important organs and tissues (target region) following the emission from radionuclides retained in body organs and tissues (source region). SAFs are computed for a series of discrete photon, electron, and alpha energies that can be convoluted with the emitted radiation spectrum, for an extensive set of source/target organ pairs. For neutrons, SAFs are provided for the full spectra of a few selected radionuclides undergoing spontaneous fission. For internal dosimetry, the influencing parameters are the relative position of the source and target organs (for penetrating radiation subject to so-called cross-fire) and organ mass (for non-penetrating radiation) [14, 42, 43]. For the specific case of alpha particles and electrons that have a very short range in biological tissues, work has focused on microcomputed-tomography-based models of electron and alpha particle dosimetry of skeletal tissues, the human respiratory tract, and the human alimentary tract (see review in [44]).

5. Radiation and Tissue Weighting Factors

The conversion from the absorbed dose to equivalent dose and then to effective dose is obtained using radiation weighting factors and tissue weighting factors, respectively. Weighting factors for radiation are derived from RBE which represents the ratio of an absorbed dose of a reference radiation (X-rays, ^{60}Co gamma radiation) to the studied radiation dose generating the same biological effect (see review in [45]). RBEs are influenced by many factors including the biological endpoint, the quality of the radiation (i.e., energy and linear energy transfer [LET]), and experimental conditions such as the dose, the dose rate, and, more generally, the duration of exposure [46–49]. There are many available experimental data on RBE, describing therefore the relative toxicity of the different types of radiation. Data were obtained under *in vitro* or *in vivo* studies, using animal or human material, and given for different endpoints, including, for *in vitro* studies, cell killing, chromosomal aberrations and mutations, and for *in vivo* studies, cancer induction, organ dysfunction, life shortening, and lethality [45].

For the purpose of radiological protection, the RBE values, which are scientific and highly variable quantities, are transformed by convention into fixed and invariable management quantities, the radiation weighting factors w_R [6]. They are derived from RBE for stochastic effects, since these effects are the most likely to occur in the dose range of interest for

radiation protection, i.e., those to the general magnitude of the dose limits. The radiation weighting factors, w_R, are then given for photons, electrons, muons, protons, charged pions, alpha particles, fission fragments, heavy ions, and neutrons and range from 1 to 20 [6]. They are to be used only for the calculation of equivalent and effective dose. In special circumstances involving high doses that can cause deterministic effects, the relevant RBE values are applied to obtain a weighted dose. The latter case also applies to the protection of non-human biota.

Tissue weighting factors are designed to represent the contributions of individual organs and tissues to overall radiation detriment from stochastic effects [6]. Radiation detriment is a multidimensional concept, calculated as an adjusted excess risk from radiation exposure, and determined from the lifetime risk of cancer and heritable effects and from an average over different populations, sexes and age at exposure, taking into account the severity of the disease in terms of lethality, quality of life, and years of life lost. Calculated values for individual organs/tissues or group of tissues are added up to give the total radiation detriment. Although relative detriments for each organ are very variable and, because of uncertainties associated with their estimation, the ICRP selected a very simplified system of weights, which used just four groups of weights that apply to both sexes and all ages. As for radiation weighting factors, tissue weighting factors represent values for management and must be used for the calculation of effective dose only [6].

6. Conclusions on the State of the Art

All the data and models described in this section are to be used for the determination of the CED, which is the main tool in internal dosimetry making it possible to apply the principles of optimization and limitation. To date, biokinetic and dosimetric models are available for the most encountered situations and enable the assessment of the doses after intake by acute or chronic inhalation, ingestion or transfer through the skin, and for workers or members of the public. The easiest tool to use is the dose coefficients, given for different chemical forms and for different ages, covering occupational and public exposures and different intake pathways. When the intake is unknown, dose per content functions are used to calculate the CED directly from the activity measured in the body or in excreta. All these coefficients provide an easy and reliable means of calculating doses and therefore managing exposures. These coefficients were revised several times since

their first publication, to take into account the latest available scientific data. The current revision led recently to the production of the OIR series [7, 9–12] and will make available a series of publications addressing intakes by members of the public, with data given for about 1,250 isotopes and for many different chemical forms.

Gaps That Would Need Improvements

Despite the use and usefulness of the tools described above, some limitations might weaken the system or at least make it subject to criticism. These gaps may be intrinsically linked to the concept of effective dose itself, which is not primarily established to assess an individual risk, or simply to lack of knowledge and data gaps in toxicology or dosimetry. The following paragraphs describe the main shortcomings in this field and the advances that could be made, either to achieve better accuracy of the CED for the reference person, or for an individualized assessment of the dose received by individuals, particularly during examinations or treatments carried out in nuclear medicine.

1. Towards More Accurate Determination of the CED for the Reference Person

1) Gaps in biokinetics

(1) Uncertainties and variability

The first gap linked to biokinetic models is due to the uncertainties of the models and individual variability. Uncertainty refers to the lack of knowledge of a central value for a population, and variability refers to quantitative differences between different members of a population [48, 50–52]. Uncertainties can come from the parameter values of the model but also from the model structure. Such uncertainties may arise because the structure provides an oversimplified representation of the known processes, because unknown processes have been omitted from the model, or because part or all the model formulation is based on mathematical convenience rather than consideration of processes. Reviews of the sources of variability and uncertainties have been published elsewhere [48, 50–52].

For purposes of radiological protection, i.e., optimization and demonstration of compliance with dose limits, these models are regarded as reference tools that are not subject to variability or uncertainty. Models are for reference workers or for reference persons at different ages and represented by a given anatomy. When these models are used in other areas such as toxicology, pharmacology, medicine, and dose reconstruction for epidemiological studies, uncertainty and variability need to be considered.

(2) Missing data for some radionuclides

Biokinetic models are based preferably on human data when available. Some degree of this type of direct information is available for most essential elements, as well as for some important non-essential elements, such as cesium, lead, radium, uranium, americium, and plutonium [48].

In cases where information is missing, data on animals and on chemical analogues may be used as surrogates. Interspecies extrapolation of biokinetic data is based on the concept of a general biological regularity across the different species with regard to cellular structure, organ structure, and biochemistry. However, despite the broad structural, functional, and biochemical similarities among mammalian species, interspecies extrapolation of biokinetic data has proven to be an uncertain process. Similarly, biokinetic models for elements are often constructed partly or wholly from data for chemically similar elements, on the basis of empirical evidence that chemical analogues often exhibit close physiological similarities (e.g., the alkaline earth elements) [26]. There are, however, several counterexamples to the premise that chemical analogues are also physiological analogues [48].

There is a great need to fill the gap due to the lack of data for some elements, such as for most of the lanthanides or other elements such as francium, in order to build models that would better describe their actual behavior in human organisms.

(3) Missing data for materno-fetal transfer and for transfer by milk

Biokinetic models describe the deposition and transfer of elements in adults and infants at different ages. An attempt was also made to describe the transfer from the mother to the embryo and fetus and from the breast milk to the nursing infant. The processes involved in transfer from maternal to fetal blood through the placenta include simple diffusion, facilitated transport, active transport, movement through pores and channels, and pinocytosis [30]. Radioisotopes of elements that are required by the developing embryo/fetus will follow the normal pathway for that element (e.g., Na, K, Ca, and Fe). For other elements, the rate of transfer will depend upon their chemical affinity for the different transport systems in the body and in the placenta, and the extent of the

result may be difficult to predict. There are sufficient human data for tritiated water, cesium, iodine, and alkaline earth to provide the basis for specific models. For the other elements, the absence of data led to a generic approach based on studies in experimental animals giving the average concentration of radionuclides in fetal tissues, C_F, and maternal tissues C_M. The relative concentration ratio C_F/C_M can be used as a conservative approach but also entails many uncertainties in the resulting dose coefficients [30]. There is a need to get more data on the initial uptake of the radionuclide by fetal and maternal tissues and placenta following its entry into maternal blood, the extent to which activity is deposited in maternal tissues and subsequently translocated to the fetus, and its retention in the developing fetal tissues, placenta, and maternal tissues.

Transfers from maternal milk to the nursing infant are described using adapted models provided initially for adults. For the recycling models, including those for the alkaline earth and actinide elements, they were extended by the addition of transfer coefficients from blood to breast and milk. For the non-recycling models, a second transfer compartment had to be added to the models. Data supporting these lactating models come from human and animal data. The milk transfer of elements such as H, C, Na, Mg, P, S, and K is very well known, and the data fully support the production of models for the radioisotopes of these elements. For other elements such as Zr, Nb, Ru, Te, Ce, Po, Th, or the actinides, the data are too sparse or come only from a few animal experiments [31]. Additional data on milk transfer of these elements need to be produced to make all these models more accurate.

(4) Models for radiopharmaceuticals

Radiopharmaceuticals administered to patients deliver doses that need to be controlled. These drugs are made of a radionuclide bound to a specific vector, which governs its deposition in the body. Thus, the usual models presented for chemical forms found in nuclear workplaces or in the environment cannot be applied. Specific models are needed for at least the most common radiopharmaceuticals used in nuclear medicine and clinical research. There are more than a hundred radiopharmaceuticals currently used in many applications, where the radionuclide may be in ionic form, organic molecules or present as labelled cellular preparations [53]. For most of these compounds, published data on biokinetics in humans are scarce [54]. Clinicians are often

interested in the initial distribution of a substance, whereas for dosimetric calculation, long-term retention in target organs is of prime importance. There is also a need to obtain information on the turn-over of the radiopharmaceutical and its metabolites, their intestinal absorption for orally administered compounds, and their final distribution in every tissue.

Another difficulty with these models is that radiopharmaceuticals are administered to patients, who can widely differ from the reference person defined by ICRP in terms of age, sex, size, and metabolic functions. These elements need to be included in the production of the models, and a significant effort is needed on the subject. ICRP is currently working on the revision of the previous models and dose coefficients provided in 1988 for 120 specific radiopharmaceuticals [53] and added to over the years [54–57]. However, the new report to be issued will provide data for diagnostic application, based on generic models built for reference individuals. They cannot be used in case of therapeutic applications for which patient-specific dosimetry based on individual dose planning is required.

(5) Models to be used under medical treatment

Biokinetic models provided for the assessment of internal doses are designed for a reference worker or reference person, assuming that the toxicity of the compound would not impair the physiology of the contaminated individual and that no medical treatment that could change the behavior of the radionuclide is administered. In nuclear workplaces, workers contaminated with radioactive substances usually receive a medical treatment either to prevent the penetration of the radionuclides into the body or to increase its excretion. Several drugs are used for this purpose, which are usually radionuclide-specific. As an illustration, stable iodine is administered to block the radioactive iodine deposition in the thyroid. Water is given to people contaminated with tritium, Prussian blue is given to people contaminated with cesium, and chelating molecules, such as trisodium salt form of calcium diethylenetriamine-pentaacetate (CaNa3-DTPA), are administered to treat most of the other contamination cases [58].

Chelating agents strongly bind to most of the radionuclides and enhance their excretion. This is not included in the models used to calculate the CED, and, therefore, any attempt to calculate the intake or the dose from the activity in excreta or in organs from a human treated with a chelating agent may

provide wrong assessments. Specific models need to be developed for this purpose. Some models are already available, such as those for DTPA bound to plutonium [59, 60], but a generic model, which would describe the biokinetics of the radionuclides after therapy and could be used for accurate dose assessment, is still missing. One of the many problems for the understanding and modeling of DTPA decorporation therapy is the still unknown sites of chelation and the identification of the bio-ligands and other molecules competing for the DTPA or the radionuclide binding [61]. A deep understanding of the underlying processes is needed for further development of these models.

2) Gaps in the weighting factors

As stated above, tissue weighting factors w_T are designed to represent the contribution of individual organs and tissues to overall radiation detriment from stochastic effects. This implies that every tissue needs to be clearly identified with respect to its risk of developing a cancer or inducing heritable effects. For these effects, the target cells are defined as homogeneously distributed in most of the organs, except in the cases of the human respiratory tract, the alimentary tract, the urinary bladder, the skeleton, and the skin, for which doses are calculated to specific cell layers. The need to supplement this list with other organs with complex internal structures (e.g., inner medulla and surrounding cortex in kidneys, adrenal glands, testes, prostate; grey and white matter in the brain) may be investigated.

For some tissue reactions (e.g., deterministic effects), the location of target cells is not yet defined for dosimetric purposes. Dosimetric targets need to be better identified and specified in the phantoms being developed, considering tissue, sex, and age dependence. For diseases involving multiple organs, such as diseases of the circulatory system, consideration of multiple targets may be investigated, based on the evolution of knowledge on the biological mechanisms.

Radiation weighting factors w_R are derived from RBE, which are highly variable data. In order to make the system easy to use, radiation weighting factors were fixed to a small set of values. Although the approach was laudable, two problems should be noted.

The first is the use of one single value for all the beta radiation (electrons). RBEs for electrons, protons, and alpha particles increase with LET, reaching a maximum at an LET of about 100–200 keV/μm, and subsequently, falling for higher values of LET [62, 63]. This maximum value of 100–200 keV/μm is

similar for a wide variety of mammalian cells and for different endpoints such as mutation and cell killing. Electrons exhibit a wide energy range, starting at one end with Auger and their typical energy of about 20–500 eV and ending with high-energy beta emitters having a maximum energy of several MeV. This variation of several orders of magnitude in energy induces a large variation in LET and thus a similar variation in RBE, with the Auger and low-energy electrons being the most efficient [64]. This wide variation cannot be reasonably represented by a single weighting factor for radiation and this issue would need to be specifically addressed.

The second problem with the electrons is when they are emitted from a radionuclide which is not distributed homogeneously in tissues. Some organic molecules such as the DNA precursors labelled with tritium or some other radiopharmaceuticals bound to low-energy beta emitters may bind to the nuclei of the cells. This binding close to DNA, combined with the fact that the electrons deliver almost all their energy in a very short range, increases the potential toxicity of these specific forms, compared to other chemical forms widely distributed in the cells, for which a large part of the dose will not be given to the DNA. This specific situation is not covered yet because the biokinetic models and the effective dose are not applicable to the use of labelled DNA precursors. This, however, needs to be considered in the future since these molecules are widely used.

2. Towards an Individualized Assessment of the Dose Received by Individuals

The effective dose was a concept created at a time when the main priority was focusing on the exposure of workers. After the Chernobyl accident, the need arose to include members of the public in order to account for the exposure of populations in contaminated territories. Since that time and the upsurge in medical examinations and treatments using radiation, the need to assess the risk to patients has become a new priority. This cannot be achieved through effective dose, which is constructed to represent the dose of a reference person, but rather through individualized dose, considering either special exposure situations or the anatomical and physiological details of the persons concerned [65]. Three examples are given below on this subject.

1) Individual dosimetry in medicine

Patients are individuals and may be very different from the reference persons. Some patients have impaired physiologi-

cal function, or even have organ ablation (e.g., thyroid, kidney, prostate, etc.) which are not modeled in the current biokinetic models. Moreover, some examinations are conducted only for patients of a specific sex (like mammography, or diagnosis of prostate cancer) and the models averaged between sex and using the reference person anatomy and metabolism cannot be used. New models considering these situations need to be produced, for a better assessment of doses resulting from exposure to radiopharmaceuticals.

These new models will allow better prediction of the deposition and transfer of radionuclides but must also be accompanied by a large set of improvements making it possible to aim at a personalized dosimetric estimate; this is essential in medicine, particularly when doses are high, and the practitioner must assess the ratio risk against the benefit of the intervention.

A personalized assessment of the dose requires at least the availability of personalized phantoms or, failing in that, a large library allowing a choice of the phantom best suited to the patient's morphology. These phantoms should make it possible to calculate the absorbed dose, which should be the reference quantity for medical procedures. However, if, for certain purposes such as justification or optimization, a calculation of the effective dose were required, then it would be appropriate not to use radiation weighting factors but to use an RBE closest to the data in the literature for the radionuclide/vector pair considered and, of course, for the effect we are seeking to avoid. Likewise, tissue weighting factors which are averaged over age and sex should not be used, but rather risk coefficients for each organ and tissue determined for specific ages and for both sexes. In all these cases, the dose thus calculated would no longer be the effective dose but a magnitude which would consider the overall dose of the whole body and would approximate to an individual dose.

2) Doses in case of emergency

As stated above, the effective dose is for reference persons, exposed to a limited set of situations and in the range of low to moderate doses. In an emergency situation, several needs may arise ranging from dose determination to specific target organs (e.g., thyroid) to prospective and retrospective individual dose assessment as well as assessments for population groups. The requirement is to define approaches that consider both stochastic effects and tissue reactions, situation-specific conditions such as thyroid blocking or contaminated wounds, and individual characteristics (such as io-dine-deficient diet in the affected region, for example). There is also a need to consider appropriate target tissues and/or regions within tissues in relation to tissue reactions. More research is required to develop appropriate approaches and systems of response.

3) Cellular and molecular dosimetry

Radiopharmaceuticals may, depending on the carrying molecule, bind to some specific targets in the body and therefore to some specific cells. Similarly, contamination with labelled nucleic acid precursors, such as tritiated thymidine, leads to a concentration of energy on the DNA in the cells. In dosimetry, it is important to define as well as possible the targets sensitive to radiation so as to calculate as accurately as possible the energy deposited there during the radionuclide decay. This is why ICRP proposes to calculate the doses to whole organs when the radionuclide distribution and that of sensitive cells are homogeneous. On the other hand, it also proposes to calculate the dose to specific target cells in the case of heterogeneous tissues, such as the lung, the digestive tract, the urinary bladder, and the skeleton. In the case of a specific intracellular distribution of a radionuclide, it would be logical to apply the same reasoning and to calculate the dose specifically received by the DNA, which is considered to be the most sensitive molecule with regard to the risk of occurrence of stochastic and deterministic effects.

This can be perfectly achieved by current computer codes such as GEANT 4, whose refinement continues to grow [66]. On the other hand, when doing this, it must be remembered that a dose, to be usable, must always be linked to an effect. A dose to the DNA may be linked to an effect on DNA but unfortunately not to an effect on a higher level of organization (cell or organ) because DNA repair mechanisms are numerous, and there is no one-to-one link between a molecular effect and a cellular effect. The same problem prevails for the cellular effects which are not necessarily correlated with the tissular effects, because of the regulation faculties (apoptosis and cell renewal) which prevent any direct relationship between these two categories of effects. Therefore, calculating a dose at the molecular level will not, at least in the near future, help pinpoint the effects at organ levels, let alone in the whole organism. These dose calculations at the cellular and molecular levels must therefore be seen as very useful tools in the field of research or even in toxicology but cannot yet be used to improve our system of calculating the individual dose.

Conclusion

The methods and tools for internal dosimetry were developed several decades ago and their reliability has been demonstrated. They make it possible to quickly calculate, prospectively or retrospectively, the CED received by workers or members of the public and to apply the principles of optimization and limitation of exposure. The parameters for the models used are constantly being revised, in order both to consider many exposure situations (different chemical forms and radionuclides) and to better represent the anatomy and physiology of organisms in the models. The usefulness and reliability of all these tools and models are well established, and they are comfortably sufficient in most situations. Refinements can still be expected on certain points of the models, such as radiation weighting factors for the beta particles and models for radiopharmaceuticals.

At the same time, there is a growing need to calculate personalized doses, in particular for medical applications. The means of calculation to determine these individual doses exist and can be deployed with some improvements. The calculated dose will not be the effective dose since it meets very strict criteria, but this point can be resolved quickly. On the other hand, it should be remembered that the calculation of a dose to an individual owes its interest, above all, to its link with a health effect. Calculating a personalized dose is therefore of real interest only if we are at the same time able to calculate with as much precision as possible the risk for the person of developing such a pathology. This therefore requires the integration of individual risk factors into the calculation, such as lifestyle habits but also antecedents or genetic factors. This means that if progress is made in the field of dosimetry, it will have to be accompanied by similar progress in the field of individual risk assessment.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

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